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Screening for Wilms Tumor in Children With Beckwith-Wiedemann Syndrome or Idiopathic Hemihypertrophy

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Background. Children with Beckwith-Wiedemann syndrome and idiopathic hemihypertrophy (BWS/HH) are at increased risk for developing Wilms tumor and screening with abdominal sonography is frequently recommended. However, there is a paucity of published data supporting this strategy. The purpose of this study was to determine whether sonographic screening at intervals of 4 months or less reduced the proportion of late-stage Wilms Tumor (WT) in children with BWS/HH. ***Procedure.*** A case series analysis was employed to compare the proportion of late-stage (stage III or IV) Wilms tumor in patients with BWS/HH who were screened with sonography (n = 15) to the proportion of late-stage Wilms tumor in unscreened patients with BWS/HH (n = 59). Patients were identified from the BWS Registry and from previously published studies. Screened patients had sonograms at intervals of 4 months or less. ***Results.*** None of the 12 screened children with Wilms tumor had late-stage disease, whereas 25 of 59 (42%) of unscreened children had late-stage Wilms tumor, a difference that was statistically significant ($P < 0.003$). Three children had false positive screening studies. They were operated on for suspected Wilms tumor but the lesions proved to be complicated renal cysts (n = 2) or nephroblastomatosis (n = 1). ***Conclusions.*** This study suggests that children with BWS/HH may benefit from screening sonograms at intervals of 4 months or less. However, false positive screening exams may result in unnecessary surgery. Given the rarity of BWS/HH, a larger, prospective international screening study is necessary to determine if the benefits of screening outweigh the risks. Med. Pediatr. Oncol. 32:196–200, 1999. © 1999 Wiley-Liss, Inc.

Key words: hemihypertrophy; Wilms tumor; ultrasound; cancer screening; epidemiology; cancer

INTRODUCTION

Children with Beckwith-Wiedemann syndrome (BWS) and idiopathic hemihypertrophy (HH) have an increased risk (estimated at 4%–10%) of developing embryonic tumors, including Wilms tumor [1–5]. Screening with sonography has been suggested as a method of identifying Wilms tumor while it is still at an early stage. However, no consensus has been reached regarding the value of periodic screening or the interval at which such screening should take place. Recommendations have been based on expert opinion [5], case reports [6,7], and two large retrospective studies [8,9]. The strongest evidence supporting screening at intervals of 3–4 months derives from anecdotal case reports in which Wilms tumor developed within the 3- or 4-month screening interval [6,7]. Others have suggested that screening may not be effective [8,9]. For instance, Craft et al. [9], using a population-based study, found no benefit to screening for Wilms tumor in BWS, HH, and aniridia. However, that study did not utilize a standard screening interval (screening intervals varied from less than 3 months to 12 months), nor did it employ uniform screening modalities (methods of screening included sonograms, physical examinations, and excretory urography). Similar limitations apply to the other retrospective analysis of Green et al. [8].

To address this issue, we compared the rate of advanced (stage III or IV) Wilms tumor in BWS/HH children who had undergone systematic sonographic screening at intervals of 4 months or less to those who had not been systematically screened.

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TABLE I. Summary of Data Demonstrating That All Screened Patients With BWS/HH Had Low-Stage* While Nonscreened Patients Had a Lower Rate of Low-Stage Disease

	Stage of Wilms tumor					
	I	II	III	IV	V	Total
Screened	8	1	0	0	3	12
Unscreened	24	9	12	12	1	59

*I, II, or V, each tumor 1-1.

MATERIALS AND METHODS

Screening was defined as an abdominal sonographic evaluation of diagnostic quality every 4 months or less (range, 2.5–4 months), which encompassed, at a minimum, the kidneys, liver, and spleen. Screened patients were derived from two sources (Table I). Fourteen of the 15 screened patients were identified from the Beckwith-Wiedemann Syndrome Registry established at the National Cancer Institute. Patients were referred to the BWS Registry by parents, pediatricians, geneticists, and the BWS Support Network [10]. The BWS Registry includes 156 patients varying in age between newborns and 32 years. The patients in the BWS Registry did not overlap with the report by Green et al. [8], which was an additional source of data for this study. The registry included 14 screened patients with suspected WT (3 patients did not prove to have WT) and 11 unscreened patients with WT. Each parent of a child in the registry completed an informed consent, a questionnaire, and an information release form. Assent was obtained in older patients. The diagnosis of BWS was based on the presence of two of the five most common features of BWS [11]: macroglossia, birth weight and length greater than the 90th percentile, hypoglycemia in the first month of life, ear creases or ear pits, and abdominal wall defect (omphalocele, diastases recti, umbilical hernia). An additional screened BWS patient came from the series published by Craft et al. [9]. This patient was identified from a larger group of children with Wilms tumor and BWS/HH. The children identified in Craft et al. [9] were from the National Registry of Childhood Tumors maintained by the Childhood Cancer Research Group in Oxford, England, since 1971. A questionnaire was sent to the primary physician of each child to confirm the diagnosis, dates of cancer, dates of screening procedure, and types of screening procedures [9]. Thus, a total of 15 patients met the criteria for systematic screening.

Unscreened patients with Wilms tumor were defined as patients who did not have imaging studies or who had imaging at intervals greater than 4 months prior to the diagnosis of Wilms tumor. Unscreened patients in this series were derived from three sources. Green et al. [8] previously published 25 patients with BWS/HH. These patients were registered in the National Wilms Tumor Study I–III and information regarding imaging prior to diagnosis was provided on the registration card and family questionnaire. All patients with HH had this diagnosis made prior to the diagnosis of Wilms tumor. Craft et al. [9] previously published 23 unscreened patients with Wilms tumor and BWS/HH. The BWS registry supplied 11 previously unpublished unscreened patients with Wilms tumor and BWS/HH to the series. There was no overlap of patients among these three groups.

The National Wilms Tumor Study Group's definition of Wilms tumor staging was employed [12]. Stage I tumors are confined to the kidney and completely removed surgically. Stage II tumors extend beyond the kidney but still can be completely excised. Stage III tumors are defined as suspected or observed residual disease confined to the abdomen after radical nephrectomy. This includes positive hilar lymph nodes, peritoneal contamination, or inability to resect the tumor completely. Stage IV is defined as the presence of hematogenous metastases. Stage V is defined as bilateral renal involvement. Stage V can be substaged (I to IV) based on imaging and surgical findings of each lesion. Stage V patients were only considered for analysis in this study if details of their local stage were known. Three of three screened patients with stage V were substaged as 1-1, and one of four unscreened patients with stage V was substaged 1-1. The three other stage V lesions were not included in this analysis because their substaged status was not known.

An assessment of tumor stage was made in all cases based on medical records. Children were divided into two groups, early- and late-stage Wilms tumor corresponding to stage I –II and III–IV, respectively. An assessment of tumor diameter was also made in both groups when measurements were available.

The chi-square test was used to determine if there was a statistically significant difference between the proportion of late-stage Wilms tumor in the screened vs. the nonscreened group [13]. The expected proportion of children with late-stage Wilms tumor was determined from the nonscreened group.

RESULTS

A total of 15 children with BWS/HH had renal masses identified by routine sonography performed at intervals of 4 months or less. Twelve of these children had Wilms tumor and all 12 had early-stage disease (Table I). Three other screened children with renal masses proved not to have Wilms tumor and are discussed in detail below.

None of the children who were screened had late-stage Wilms tumor. Stage distribution of Wilms tumor among the children who were screened was as follows: stage I, 8; stage II, 1; stage III, 0; stage IV, 0; stage V substage 1-1, 3. All screened children had BWS. Of the 59 unscreened children with Wilms tumor and BWS/HH stage

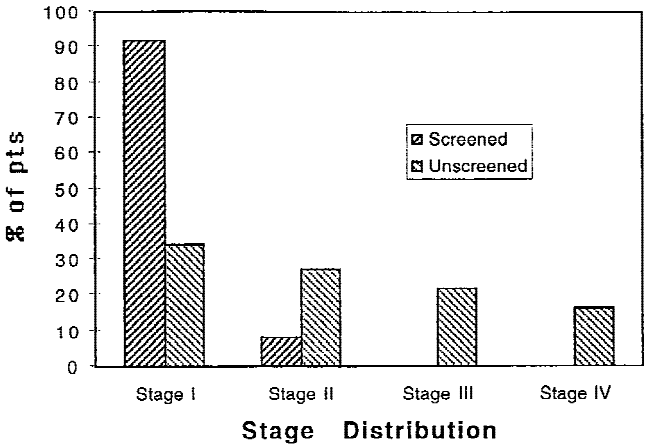

Fig. 1. Stage distribution of Wilms tumor for screened and unscreened patients with BWS/HH. Stage V Wilms tumor were substaged 1-1 and are included in stage I.

distribution for Wilms tumor was as follows: stage I, 24 (BWS = 10, HH = 14); stage II, 9 (BWS = 5, HH = 4); stage III, 13 (BWS = 2, HH = 11); stage IV, 12 (BWS = 2, HH = 10); stage V, 1 substaged as 1-1 (BWS = 1). The difference between the proportion of children with late-stage Wilms tumor in the screened group 0/12 (0%) and unscreened group 25/59 (42%) was clinically relevant and statistically significant ($P < 0.003$) (Fig. 1).

The diameter of the Wilms tumor was available for 11 of 12 screened patients. The average size of Wilms tumor in this group of children was 3.4 cm (n = 11, SD = 2.0). Since the majority of patients in the unscreened group were obtained from a retrospective review and tumor size was not recorded, it was not possible to estimate the size of Wilms tumors in this group.

Three patients from the BWS registry were screened with sonograms at 4-month intervals and were found to have renal masses that proved not to be Wilms tumor. Patient 1 was a 1-year-old girl who had an echogenic mass about 2 cm in diameter that was stable on two consecutive screening studies. Because Wilms tumor was suspected, an exploratory laparotomy was performed. An intraoperative ultrasound revealed that the lesion was cystic. Pathologic examination of the resected lesion revealed an infected renal cyst. Patient 2 was an 8-month-old boy who demonstrated a cystic lesion in the upper pole of the left kidney on a screening sonogram that enlarged over a period of 6 months. A CT was performed and was interpreted as representing a Wilms tumor even though it was quite cystic. He underwent a left radical nephroureterectomy on the presumption that the lesion was a Wilms tumor. It proved to be an infected renal cyst. Patient 3 was a 2-year-old boy who was determined to have a solid renal mass on screening sonography. A CT of the abdomen was performed, suggesting either nephroblastomatosis or Wilms tumor. A radical nephrectomy was performed and revealed nephroblastomatosis with no evidence of Wilms tumor. The contralateral kidney was normal by sonography, CT, and visual inspection at the time of surgery.

DISCUSSION

Screening for Wilms tumor in children with BWS/HH is controversial. A potential benefit of screening is to identify the tumor early when surgery alone is curative and thus decreases the long-term sequelae associated with radiation and anthracycline chemotherapy, which are required to treat advanced-stage Wilms tumor [14]. However, no studies have documented the effectiveness of sonographic screening in detecting early-stage WT; on the contrary, there have been studies suggesting no benefit to this strategy [8,9].

Our case series suggests that screening at intervals of 4 months or less can significantly reduce the proportion of late-stage Wilms tumor. This is supported by evidence that the mean tumor diameter is less for screened patients than for patients with sporadic Wilms tumor. For instance, the average tumor diameter was 3.4 cm for screened patients in this series, while the average tumor diameter in two other series of sporadic Wilms tumor was 11 and 13 cm, respectively [15,16]. Based on the finding of a lower proportion of children with late-stage Wilms tumor and smaller tumor diameter, we believe systematic screening may be beneficial. With these data, it is not possible to state that 4 months is the ideal screening interval since this was only the maximum interval tested. Ultimately, a prospectively designed screening intervention trial will be needed to determine whether screening is warranted and at what interval it should be performed.

Besides our study, evidence in support of screening at 4-month intervals is anecdotal. In one published case of a patient with BWS, a Wilms tumor was discovered 3 months after a negative surgical inspection of the kidney [6]. Woodard et al. [17] also described a child with BWS who presented with symptomatic disease 4 months after a negative imaging study. In another case, Andrews et al. [7] described a child with BWS who had sonograms every 3 months and developed an interval Wilms tumor measuring 3.5 cm in diameter. We are aware of two other children who developed large (7-cm and 15-cm diameter) stage I Wilms tumor within several months of a negative evaluation and presented with an abdominal mass in both cases and hematuria in one case (Dr. Daniel Green, personal communication). Taken together, these observations suggest that an appropriate interval for screening for Wilms tumor is between 3 and 4 months.

Our analysis differs from the two previous studies on

the effectiveness of screening for Wilms tumor in children with BWS/HH [8,9]. These studies did not define a specific screening interval, nor was there a standard screening regimen. Screening studies in these series included physical examination, excretory urography, as well as sonography, each of which vary in their sensitivity for detecting Wilms tumor [8,9]. By comparison, we assessed only a single imaging modality, sonography, at a relatively fixed interval of 4 months or less.

A major consideration when assessing a Wilms tumor screening program is the impact of false positive results. In our series, three children underwent laparotomies for suspected Wilms tumor and nephrectomies were performed in two. These cases illustrate several potential pitfalls associated with screening. First, additional imaging studies beyond the initial screening sonogram were not performed in one case. Currently, we recommend that an enhanced CT or MRI examination with 5-mm-thick sections be performed in patients with a suspicious renal lesion on sonography prior to surgery [18]. This may prevent further diagnostic evaluation or at least guide additional treatment, especially if the lesion is documented to be a cyst. Second, it appears that additional diagnoses such as cysts or abscesses were not considered in the differential diagnosis and this may have contributed to the decision not to perform further testing to clarify the nature of the lesion. Third, when there is a consideration of nephroblastomatosis, an open biopsy rather than nephrectomy may help differentiate between a premalignant and malignant condition and thus spare the kidney.

As with all case series, our study has limitations. Unfortunately, the number of screened patients with Wilms tumor is small. This reflects the relative rarity of BWS/HH and Wilms tumor. Even though Wilms tumor is common (10%) in patients with BWS/HH [19], the overall frequency of BWS is still low (1:12,000 births) and it is difficult to accumulate large numbers of patients. Another limitation is that it is possible that parents who participate in screening programs are sensitive to the possibility of Wilms tumor and may have a lower threshold to go to their physician for subtle symptoms. The screened patients, with one exception, came from a BWS Registry and a similar registry is not available for HH hemihypertrophy. This meant that all of the screened patients had BWS and none had HH. This limitation can only be resolved by including larger numbers of patients with both BWS and HH in prospective screening trials. In the unscreened group, most of the higher stage (III, IV) tumors occurred in patients with HH. Although we cannot be sure, we believe that patients with BWS are under closer medical scrutiny because of their multisystem involvement. As a result, they may be less likely to present with late-stage tumors than are children with HH. This bias may increase the apparent rate of late-stage tumors in patients with HH.

We have demonstrated that screening in intervals of $\leq$4 months for Wilms tumor is effective in decreasing the stage of Wilms tumor at diagnosis. However, a screening program will not be without limitations, foremost of which are false positive results, which may lead to unnecessary diagnostic and therapeutic procedures. Given the rarity of BWS/HH, a prospective international intervention trial is warranted to determine the true risks and benefits of screening in this population.

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